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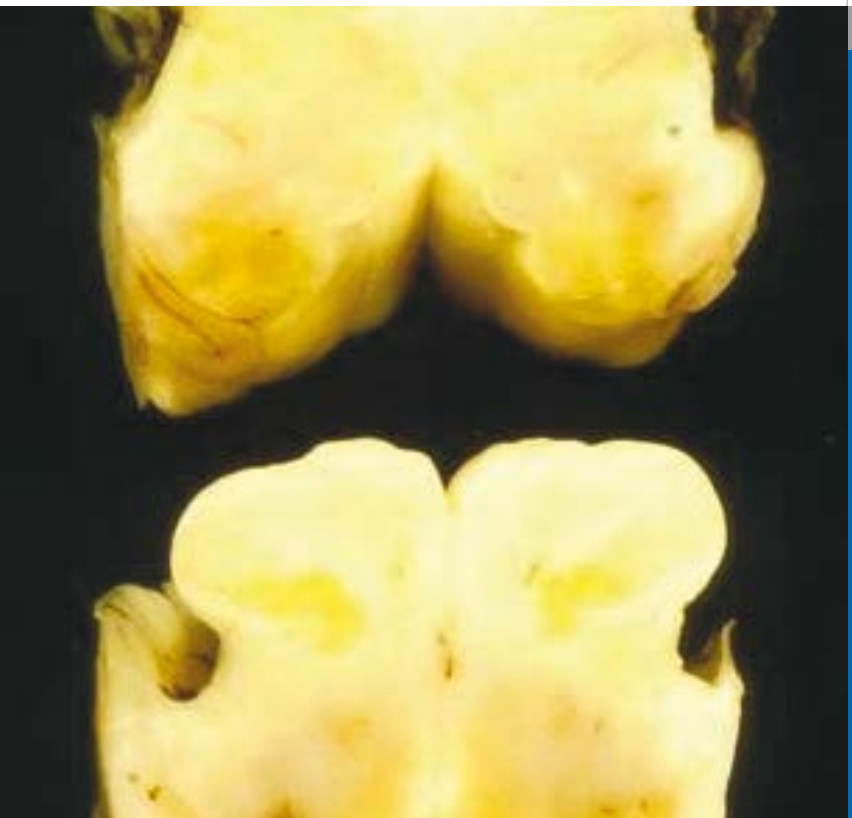
Bilirubin encephalopathy: renaissance of an ancient problem?



June 2005

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A boy was born at 38 weeks of gestation as the second child to a 31-year-old mother originating from Santo Domingo and a Swiss father. The pregnancy had been without complications apart from some minor preterm contractions at 33 weeks of gestation at which point lung maturation was induced. The Apgar scores were 4,7 and 9 at 1, 5 and 10 minutes, respectively. The baby was given some oxygen during the first minutes of life with rapid improvement. Initial clinical examination on the first day of life showed dark pigmentation due to the mother's ethnical origin and revealed no abnormalities. The baby was exclusively breast-fed without problems.

On the third day of life, the nurse noted that the baby was slightly jaundiced, but the serum bilirubin concentration was not measured. Routine clinical examination on the fourth day of life revealed that there was jaundice of the skin and even more markedly of the sclerae. At that point, the serum bilirubin concentration was 629 µmol/l (37 mg/dl) and the hematocrit was 62%. The mother's blood group was A positive, and the child's blood group was A negative with a negative direct antibody test (direct Coombs' test). On admission to our neonatal intensive care unit, the baby showed neurological abnormalities with opisthotonus and jitteriness. An albumin solution was administered until blood was available for emergency exchange transfusion. A double volume exchange transfusion was then performed twice, each time with

600 ml of blood. Venous serum bilirubin concentration was 738 µmol/l (43.4 mg/dl) at the beginning and 230 µmol/l (13,5 mg/dl) by the end of the second exchange transfusion. Phototherapy was then performed until the fifth day of life. There was no anemia.

Further investigation revealed that glucose-6-phosphate-dehydrogenase deficiency (G-6-PD deficiency) was responsible for the hyperbilirubinemia. The mother was heterozygous for G-6-PD deficiency.

Neurological signs consistent with bilirubin encephalopathy persisted: frequent crying, restlessness, jitteriness, poor feeding, apneas, muscular hypertonia with opisthotonus, alternating with periods of muscular hypotonia. Sedation with phenobarbital was initiated. The EEG showed only slight abnormalities whereas acoustic evoked potentials where pathologic. Magnetic resonance imaging (MRI) performed at the age of 14 days revealed hyperintensity in the pallidum and possibly in the nucleus subthalamicus on T1-weighted images (Fig. 1). These findings are compatible with early bilirubin encephalopathy; later, the affected areas become hyperintense on T2-weighted images. For comparison, a pathology specimen is shown in Fig. 2 (courtesy of the Institute of Pediatric Pathology, University Hospital of Zurich, Switzerland). The baby was discharged home at the age of 14 days.

The patient is now nearly three years old and shows

severe neurological impairment with the typical choreo-athetotic cerebral palsy and central hearing loss, but a normal vision. He can only walk without support for a very short distance and prefers to hold on to someone or crawl. His cognitive development is that of an 18 to 24-month-old child. His speech is poor,

Axial T1-weighted image shows hyperintensity in the region of the basal ganglia (particularly globus pallidus).

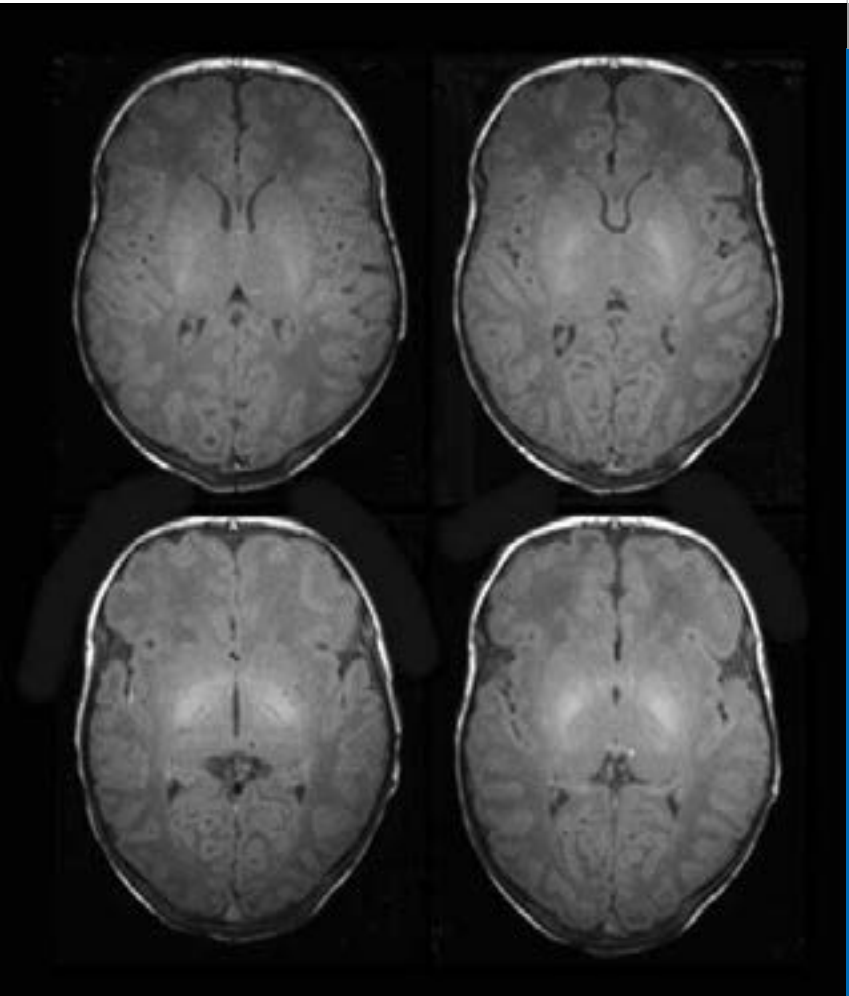

Fig. 1

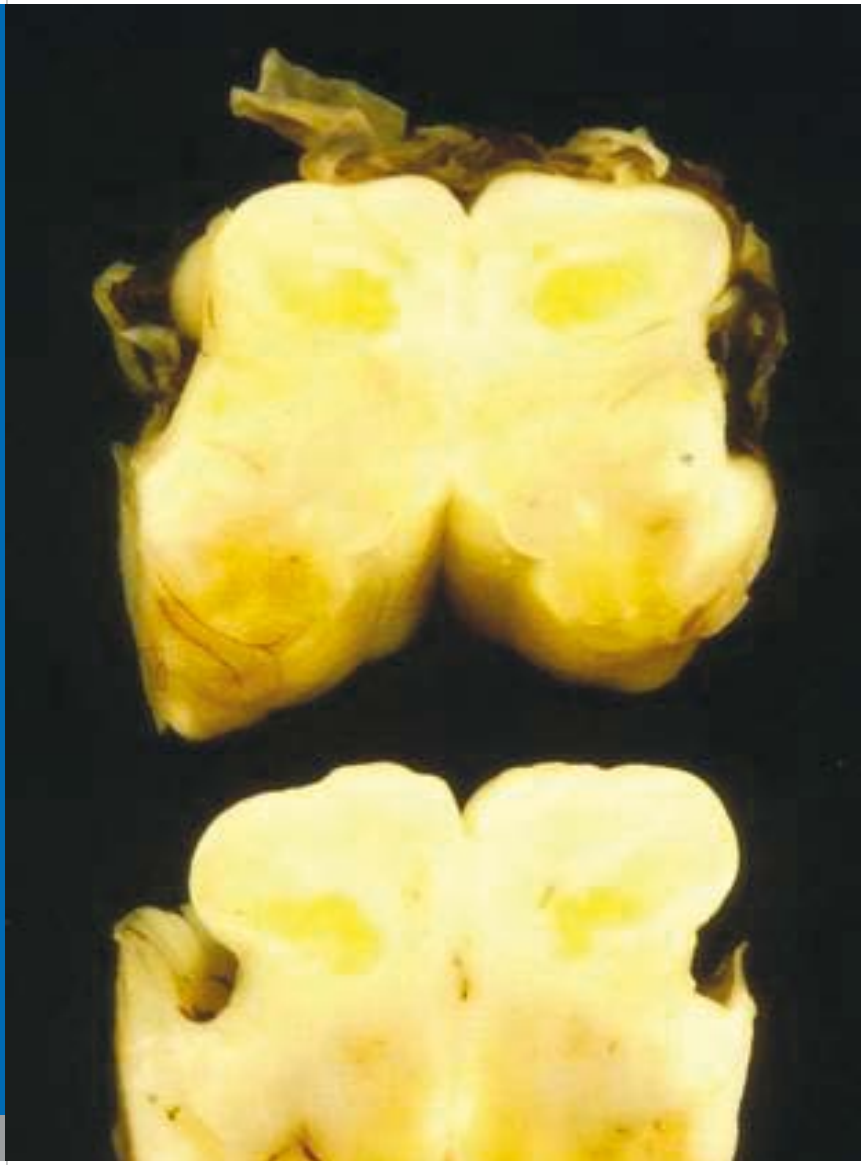

Fig. 2

Characteristic yellow staining of basal ganglia and cranial nerve nuclei in Kernicterus (from the Institute of Pediatric Pathology, University Hospital of Zurich, Switzerland).

To our knowledge, this is the first case of bilirubin encephalopathy in Switzerland in three or four decades. With the introduction of rhesus prophylaxis in 1963 by Clark-Freda, the incidence of hemolytic disease of the newborn (HDN) dropped dramatically. Combined with the earlier introduction of exchange transfusion by Diamond (1948) and phototherapy by Cremer (1958) Kernicterus was almost eradicated. The global infant mortality of this condition is estimated to be 0.7-1.6 per 1000 live births (1).

The clinical picture of neonatal jaundice related to G-6-PD deficiency differs from rhesus-related jaundice in two main aspects: first, the peak incidence of onset is later (second or third day of life), and second, anemia is not necessarily present and rarely severe. Not every newborn with G-6-PD deficiency develops neonatal jaundice. Factors that contribute to the development of neonatal jaundice related to G-6-PD deficiency are not yet fully understood. In absence of hemolysis, neonatal jaundice and G-6-PD deficiency could be associated with a mutation of the promotor region of the UDP-glucuronyl transferase as in Gilbert-Meulengracht syndrome (2) or a mutation in the gene for bilirubin-UDP-glucuronyl transferase; infections, maternal medication, nutrition or other environmental causes can also trigger neonatal jaundice.

After having almost vanished, bilirubin encephalopathy (Kernicterus) has re-emerged in the last ten years. Eb-

besen et al. (3) reported six cases of Kernicterus in Denmark between 1994 and 1998, after a period of 20 years without a single case. The total plasma bilirubin concentrations in these cases ranged between 531-745 µmol/l (31.2-43.8 mg/dl). Five of the six infants had definitive sequelae with development delay, athetoid cerebral palsy, hypertonia, hearing loss, and balance disturbances. A similar increase in the incidence of bilirubin encephalopathy has been described in the USA (4, 5). There are several possible explanations for this phenomenon. As Ebbesen [3] states, awareness of the dangers of bilirubin encephalopathy has diminished because no cases have been seen in the last few decades. The traditional opinion that Kernicterus is a disease of the past is due to an underestimation of the effects of bilirubin on the developing nervous system (Fig. 2). Neurological sequelae, especially auditory neuropathy and other central auditory processing disorders may result from excessive amount and duration of exposure to unconjugated bilirubin at different stages of neurodevelopment (6). Nowadays, jaundice secondary to G-6-PD deficiency is of major importance (7). In addition, in recent years, newborns are often discharged from hospital before bilirubin reaches its highest level, thus making measurements of bilirubin levels more difficult. Finally, dark skin pigmentation make it more difficult to recognize the onset of jaundice (8, 9).

We emphasize that it is crucial to be aware of the dangers of hyperbilirubinemia especially in infants where this condition can easily be underestimated such as in infants with dark skin, preterm infants and infants with G-6-PD deficiency. The implementation of guidelines to prevent children at risk from developing severe hyperbilirubinemia is desirable (10). The Center of Disease Control and Prevention plans to initiate surveillance and systemic evaluation of trends and prevalence rates of bilirubin encephalopathy (5).

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